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MEETING ABSTRACTS

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Proceedings of the Musculoskeletal Health in the 21st Century Workshop

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INTRODUCTION

I1

Musculoskeletal Health in the 21st Century

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In July 2015 a multidisciplinary two-day workshop entitled "Musculoskeletal Health in the 21st Century" was organised by the authors at the University of Surrey. The aim of the workshop was to bring together some of the major stakeholders including clinicians, basic scientists and funding bodies to focus on current challenges in musculoskeletal health and discuss current strategies for intervention and disease prevention. Workshop participants discussed and debated the effects of physical activity, body condition, diet and vitamins on the musculoskeletal system, focusing specifically on the synovial joint. The workshop also included sessions on joint health, arthritis prevention through physical activity (including biomechanics of musculoskeletal tissues), effects of diet and nutrition, understanding the underlying physiology and pathophysiology of cartilage and bone, prognostic biomarkers and new insights from genetic diseases of the musculoskeletal system. This Special Supplement of BMC Musculoskeletal Disorders includes a general review article summarising some of the current research in musculoskeletal health and includes abstracts presented at the July 2015 workshop in Surrey.

MEETING ABSTRACT

S1

Diabetes-induced osteoarthritis: role of hyperglycemia in joint destruction

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Recent epidemiologic and experimental data reinforced the concept that diabetes mellitus (DM) is an independent risk factor for osteoarthritis (OA). Besides a systemic inflammatory response that can affect joint tissues and contribute to OA pathogenesis, direct effects of hyperglycaemia have been shown to cause cell damage and induce inflammation by various mechanisms in several tissues associated to diabetic complications. Whether and how glucose directly affects joint tissues and cells is just beginning to be unraveled. Indirect effects of high glucose can result from enhanced formation of advanced glycation end products (AGEs) which accumulate in OA cartilage in an age-dependent manner and play a pro-inflammatory and pro-catabolic role mediated by activation of their specific receptor, RAGE, on chondrocytes and synovial cells. Some direct effects of high glucose have also been demonstrated, namely induction of IGF-1 resistance [1] and inhibition of dehydroascorbate transport which can compromise collagen synthesis [2]. Our studies have been aimed at determining whether and how hyperglycemia affects chondrocyte functions and contributes to OA development and progression. The results obtained showed that high and low glucose concentrations regulate the availability of facilitative glucose transporter (GLUT) isoforms and the glucose transport capacity of human chondrocytes. High glucose concentrations decrease the transport capacity and GLUT-1 protein content without affecting its mRNA levels, but this ability to adjust glucose transport capacity as a function of its availability is compromised in aged/OA chondrocytes leading to its intracellular accumulation [3]. The consequences of this are increased and prolonged ROS production [3] and expression of metalloproteinases (MMP)-1 and -13 [4], IL-1 β , TNF- α , inducible nitric oxide (NO) synthase (iNOS) and NO production, mediated by high glucose-induced NF- κ B activation [5], as well as decreased responsiveness to TGF- β [4] and impaired autophagy [5]. High glucose is thus sufficient to induce an inflammatory and catabolic response in human OA chondrocytes. Furthermore, it potentiates pro-inflammatory effects of IL-1 β , namely IL-6, cyclooxygenase 2 (Cox)-2, prostaglandin E2 (PGE2) and NO production [6]. The pro-inflammatory effects of high glucose in human chondrocytes and diabetic mice, namely induction of Cox-2, IL-6 and MMP-13 and production of PGE2, as well as decreased production of Collagen II, have also been shown to involve impairment of anti-inflammatory pathways, namely by decreasing PPAR- γ expression [7]. Elucidating how high glucose modulates joint tissue homeostasis will identify novel targets for development of innovative strategies both to identify diagnostic and prognostic biomarkers of OA and to effectively modify disease progression.

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S2

Biomarkers of prognosis and efficacy of treatment in OA

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BMC Musculoskeletal Disorders 2015, **16**(Suppl 1):S2

OA is a disease affecting the metabolism of all joint tissues leading to structural changes visible by imaging techniques. Unfortunately, features visible by imaging are in most cases irreversible and progressively moving towards worsening. One challenge for the next decade will be disease detection at the early stage when the first molecular/metabolic changes appear in joint tissues. Another challenge is to develop tools to assess the efficacy of OA treatment on the natural history of the disease. Therefore, there is an acute need for reliable biological markers that can facilitate earlier diagnosis of OA, predict the progression of the disease and evaluate the efficacy of therapeutic modalities.

A recent literature review resulted in the identification of 16 biochemical markers investigating cartilage matrix turnover. Nine concerned collagen type II degradation (Coll2-1, Coll2-1NO2, CTX-II, Helix-II, C2C, TIINE, CIIM) and synthesis (PIIANP, PIICP). Keratan sulphate, chondroitin sulphate 846 (CS846) and ARGS-aggreCAN fragment investigate proteoglycans degradation. Serum cartilage oligomeric matrix protein (COMP), deamidated-COMP (D-COMP), fibuline-3 fragments (Fib3-1 and Fib3-2) were the other biochemical markers that are considered as markers of cartilage matrix metabolism.

Risedronate and strontium ranelate, two drugs currently used to treat osteoporosis decreased urinary CTX-II levels suggesting that they can modulate cartilage metabolism, even if they did not alter radiological progression. However, recently, it was demonstrated that CTX-II was more strongly associated with bone markers (i.e. uNTX, uCTXI, serum PINP, and osteocalcin) than with other cartilage markers (PIIANP, sCS846, sCOMP), while the "other" cartilage markers were not so strongly associated with the bone markers. These data indicate that CTX-II might reflect bone rather than cartilage metabolism. In an exploratory study investigating the effects of three intra-articular injections of hyaluronic acid (Hylan GF-20) on the evolution of 10 biochemical markers, we have demonstrated that uCTXII, sColl2-1 and sColl2-1NO2 levels were significantly affected by treatment suggesting that these markers are sensitive to metabolic change occurring in one single joint. More recently, we have observed

that three months treatment with bio-optimized curcumin significantly decreased sColl2-1 level in 24 patients with knee OA, suggesting that sColl2-1 could be a companion marker to assess curcumin efficacy at an individual level and in the next phases of its clinical development.

Although many OA-related biomarkers are currently available they exist in various states of qualification and validation. At this time, none of the existing biomarker can be considered as a surrogate marker of clinical and imaging feature for the diagnosis or prognosis of the disease. In this context, the recent development of large cohort designed to qualify biomarker will accelerate biochemical marker implementation in clinical research.

S3

Global burden of osteoarthritis and musculoskeletal diseases

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Over the past century, global health priorities were largely focused on communicable diseases. With the world's population growth, increased average age and decreased death rates, people are now living longer and becoming increasingly susceptible to the non-communicable diseases, including musculoskeletal (MSK) disorders. The recent Global Burden of Disease (GBD) Study estimated the burden disability in 187 countries and 21 regions of the world for the years 1990, 2010 and 2013 of all MSK disorders - osteoarthritis (OA), rheumatoid arthritis (RA), gout, low back pain (LBP), neck pain (NP) and all other musculoskeletal disorders. Throughout the world, the prevalence and burden from MSK conditions were exceptionally high. All MSK disorders combined caused 21.3% of the total years lived with disability (YLDs) globally - second to mental and behavioural problems (23.2%). When taking into account both death and disability, all MSK disorders combined accounted for 6.7% of the total global disability-adjusted life years (DALYs), which was the fourth greatest burden on the health of the world's population (third in the developed countries). Out of the 291 conditions studied, LBP ranked first (highest) for the disability (YLDs), and sixth for the overall burden (DALYs). For NP, the condition ranked fourth highest for YLDs, and 21st for DALYs. 'Other MSK disorders' ranked sixth highest for YLDs and 23rd for DALYs. Osteoarthritis, RA and gout were also significant contributors to the global disability burden. In addition to this burden of disability as estimated by these summary measures of health, there is the impact on the individual's quality of life and economic independence as well as the costs to society due to health and social care and due to work loss. Despite this enormous and growing burden there is a lack of priority and of policies focusing on musculoskeletal health. This needs to change if we are to meet the demands of an ageing population that needs to be able to remain economically independent.

S4

Latest approaches on the management of OA in humans

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The Sofat laboratory currently investigates the mechanisms responsible for pain and tissue damage in arthritis. Clinical studies include 'Pain management in osteoarthritis using centrally acting analgesics' (<http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=12175>) funded by the Rosetrees Trust. This clinical trial is testing whether drugs that inhibit pain processing pathways in the brain can help with pain in the hand caused by osteoarthritis. Other clinical studies include the 'Pain Perception in Osteoarthritis', or PAPO study, investigating tissue damage and pain in people undergoing knee replacement surgery for osteoarthritis. Both studies are on the UK NIHR portfolio of network-adopted studies.

Our laboratory has a translational approach, with techniques including magnetic resonance imaging (MRI) to decipher regions of damage in affected joints and evaluating which brain regions are activated by arthritis pain. We also use non-invasive quantitative sensory testing (QST) methods to identify pain pathways. QST identifies sensation and pain thresholds by stimulating the skin.

Our laboratory research uses a basic science mechanistic approach to investigate the influence of endogenous damage-associated molecular patterns (DAMPs) in driving chronic inflammation in joints. Molecules of interest include interaction of the DAMPs tenascin-C and fibronectin with oral pathogens.

S5

Mechanisms of FAI cartilage damage: experimental & simulation studies

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Femoral acetabular impingement (FAI) is thought to be a key underlying reason for the development of osteoarthritis of the hip. There are two main types of FAI, cam-type and pincer-type. The cam-type FAI gives rise to cartilage delamination initially thought to occur on the acetabular side of the joint. The purpose of the current study was to look at the effects of cam-type impingement on the generation of shear strains at the bone/cartilage interface, using both experimental and finite element simulation methods. Sagittal slices (n=9) of femoral porcine cartilage-bone, 10 mm thick, were loaded using a five-axis custom test machine with a curved (radius 90 mm) steel indenter. The five-axis test machine allowed the samples to be subjected to compression and mixed compression/shear loading regimens. The specimen strains were measured using two dimensional digital image correlation (DIC). Each test was also simulated using finite element analysis, and the results compared with the DIC data. The specimens were then cyclically loaded either with or without damage to the cartilage layers; damage simulated clinically reported lesions. Maximal shear strain was found at the cartilage-bone interface, and was a function of compressive loading level. The finite element predictions matched the DIC measurements. The two parameters that were most important in terms of shear strain were the cartilage thickness and contact area radius. It was found that increased cartilage thickness and increased contact radius gave rise to higher shear strains. Cyclically loading the damaged specimens produced features of cartilage delamination consistent with clinical observations. The results of this study indicate high shear strain at the bone/cartilage interface is a possible mechanism leading to cartilage delamination, and may be the mechanism behind cartilage degradation in patients with cam-type FAI.

S6

Musculoskeletal health from the "One Medicine" perspective – what can we learn from large and small animal models (with emphasis on articular cartilage)?

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In human medicine musculoskeletal diseases rank (together with mental disorders) first in reasons for occupational disability and have a huge impact on both quality of life and overall healthcare costs [1]. The current increase in life expectancy, together with decreasing societal acceptance of impaired mobility, have strongly pushed musculoskeletal research in recent years. The classic animal models for research into musculoskeletal disease are small rodents, especially mice and rats. As larger species, goats and to a lesser extent sheep have been the species of choice. This choice was largely based on practical and logistical considerations such as the required size, availability, costs and ease of handling, rather than on biomedical criteria.

The growing acceptance of the "One Health, One Medicine" concept has, together with better knowledge of fundamental differences between mammalian species in articular cartilage biology and the increasing pressure to reduce, refine and replace (the three "Rs") animal experimentation, led to

a change in attitude towards the use of animal models in musculoskeletal research [2]. Whereas small rodents may still be a logical step after *in vitro* research, the fundamental differences between articular cartilage composition of smaller species and those heavier than about 1Kg [3], together with the increasing recognition of the role of biomechanics within the joint, cast severe doubts on the validity of these species for anything but very basic work in musculoskeletal research. In contrast, within the "One Medicine" concept it is clear that in veterinary medicine there are several species featuring a high prevalence of musculoskeletal disorders that are very similar to those seen in humans. This applies to dogs with intervertebral disc disease [4] and chronic joint disorders (especially osteoarthritis (OA)) in both horses and dogs [4]. These developments have led to a gradual shift in the use of animals in musculoskeletal research. Also, regulatory bodies are making this shift of mind with the US Food and Drug Administration (FDA) now requiring preparatory work in horses before approval for certain orthopaedic devices is granted.

There is one other important aspect to this development. Whereas the classic animal models were solely used to the benefit of human research, research in dogs and horses will forcibly lead to medical improvements for these species, as they are patients too and hence not only experimental animals, but target species as well. This is an important asset for the ethical justification for the use of animals for scientific research.

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S7

Diet, nutrition and osteoarthritis

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BMC Musculoskeletal Disorders 2015, **16**(Suppl 1):S7

Osteoarthritis (OA) is the fastest growing cause of disability worldwide [1]. In the absence of effective therapies, patients may wish to take some control of their own condition by making dietary changes that have the potential to ameliorate symptoms or reduce disease progression.

A number of dietary factors have been associated with OA symptoms or progression. Most notably, in those overweight, weight reduction of ≥10% has the potential to lead to important changes in pain and function [2]. Losing weight also reduces pain-associated inflammation [3]. Weight loss combined with physical activity has an even greater capacity to improve pain and function [4].

It has been suggested that OA is a metabolic disease in which lipids essentially contribute to the pathophysiology of cartilage degradation [5]. Dietary long-chain ω-3 PUFA may affect articular cartilage composition and appear to have beneficial effects in OA [5]. In a US cohort of individuals with, or at high risk of, knee OA, there was a significant inverse relationship between total n-3 PUFAs and patella-femoral cartilage loss [6]. A positive association has been shown between elevated serum cholesterol and OA; hypercholesterolemia (OR 1.61; 95% CI 1.06-2.47) and high serum cholesterol (3rd vs. 1st tertile: OR 1.73; 95% CI 1.02-2.92) were independently associated with generalized OA in the Ulm study [7]. Hence there may be a potential benefit in adopting dietary cholesterol-lowering strategies (such as consumption of sterol/stanol spreads/drinks). Vitamin D affects the state of multiple articular structures. The evidence for association between the vitamin D biomarker, serum 25(OH)D, and

OA was assessed in a systematic review. For knee radiographic OA progression and cartilage loss, there was strong evidence for an association with low 25(OH)D [8].

Vitamin K is important in cartilage metabolism as an inhibitor of extracellular matrix calcification and a promoter of cell survival/proliferation. In the US MOST study, vitamin K deficiency was associated with incident radiographic knee OA and MRI-based cartilage lesions (RR 2.39; 95% CI, 1.05-5.40) compared with no deficiency [9].

Hence, dietary recommendations are the following:

- ☒ lose weight, if overweight, preferably combined with exercise;
- ☒ reduce plasma cholesterol by dietary means;
- ☒ at least for a trial period, increase intake of long-chain n-3 fatty acids preferably by eating oily fish twice a week;
- ☒ aim for a safe level of sun exposure, eat rich vitamin-D dietary sources or take vitamin D supplements, $\leq 25 \mu\text{g/d}$;
- ☒ increase vitamin K intake by eating green leafy vegetables.

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S8

Osteoarthritis of the Knee

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BMC Musculoskeletal Disorders 2015, 16(Suppl 1):S8

Self-management (SM) programs for people with arthritis or other chronic diseases are commonplace and usually delivered by lay leaders. There is evidence indicating these programs are effective, although systematic reviews show these improvements are small.

The self-management program for Osteoarthritis of the Knee (OAK) differs from other programs in a number of aspects. It is disease-specific and tailored for people with OAK. It was developed using an ENAT survey, a collaborative approach, and a Plan Do Study Act (PDSA) model. It was planned purposely for implementation in hospitals or community settings. The program is detailed for delivery by health professionals. In

particular, exercise and disease coping strategies are promoted within a SM construct to improve quality of life and general health as well as reducing pain.

The program was tested using an uncontrolled quality assurance study and the results were positive in pain, quality of life and physical function. A randomised controlled trial (RCT) was undertaken, where, the OAK group showed statistically significant improvements when compared with the control group with regard to pain, quality of life and function on the basis of WOMAC and SF-36 measurements taken 8 weeks and 6 months from baseline.

The OAK program is conducted in a group setting over six weekly sessions of 2.5 hours. This allows participants to progress over time by incorporating and consolidating new information learned each week. In addition to the weekly sessions, handouts and reference book readings are given.

For optimum group dynamics, the program is delivered by the same two health professionals to a group of 12-14 participants. The fidelity of the OAK program is maintained by the use of a scripted facilitators' manual. Using a holistic approach, the program addresses multiple aspects of care: osteoarthritis (explanation and implications), SM skills (goal-setting, problem-solving, positive thinking and improving self-efficacy), medications (types, interactions and current trends), pain management strategies (cognitive and pharmacologic), fitness and exercise (strength, flexibility, aerobic), joint protection, nutrition and weight control, falls prevention (balance and proprioception), environmental risks, and coping skills.

The OAK program has been sustained by development of health professional training workshops. OAK programs are delivered throughout Australia primarily by physiotherapists especially those working in district hospitals or primary care settings. To reduce costs, we have recently trialled programs using self-management trained peer leaders and health professionals which has worked extremely well.

S9

Ageing in humans: separating intrinsic ageing from lifestyle effects

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We are an ageing society, with falling birth rates and increasing life expectancy. However healthy life span is not keeping pace and on average older adults can expect to be unwell for the last decade of life. Many factors influence both lifespan and healthspan but in humans one of the key factors is likely to be increasing physical inactivity. To separate out those elements of the ageing phenotype that are due to inactivity from those which are intrinsic to the ageing process, we recruited 125 adults aged 55-79 who had maintained a high level of physical activity through their adult lives. We compared these with age matched healthy older adults who were not involved in regular physical activity and healthy young subjects. The subjects were assessed for key features known to change with ageing including sarcopenia, reduced bone mineral density, adiposity, cardiovascular and lung function as well as markers of immune ageing. We have already reported the physiological data which revealed that many features of ageing including lean body mass, adiposity and muscle strength did not change with age in the physical active group, though other effects were seen such as a decline in lung capacity (FEV1) and maximal heart rate. Here we report that a comparison of immune phenotype in the exercising and non-exercising groups showed that thymic output was significantly reduced in the inactive group compared to both the young subjects ($p<0.002$) or the physically active older subjects ($p<0.009$). The numbers of naïve T cells was also maintained in the active elders, though the rise in the numbers of senescent T cells was not protected by an active lifestyle. We conclude that an active lifestyle through adulthood can prevent many of the physiological and immune features normally attributed to ageing.

S10

Non-invasive techniques for studying macrophages in joint inflammation

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Folate-based radiotracers have been used in patients with cancer and inflammatory diseases to visualize folate receptor expressing cells using PET or SPECT techniques. Activated macrophages express folate receptor beta (FR β) and this allows specific imaging of these cells *in-vivo*. From previous work using SPECT imaging to visualize folate receptor expressing macrophages in both animal models and in patients with OA we know that macrophages are present in OA affected joints. However, it remains unclear what role these macrophages play in the different stages of OA and whether their role can be influenced by specific targeting.

In Wistar rats osteoarthritis was induced using a low dose of intra-articular papain injections in one knee joint combined with exposure to a moderate exercise protocol. After six weeks and twelve an *in vivo* folate SPECT/CT scan and micro-CT analyses were performed. Macrophages from human peripheral blood monocytes were cultured (7 days) in the presence of GM-CSF (M1 proinflammatory phenotype) or M-CSF (M2 anti-inflammatory phenotype). Subsequently the macrophages were treated with LPS, cytokines (IL-4, IL-10, IFN- γ) or a corticoid steroid (triamcinolone acetonide, 1 μ g/ml). Folate receptor beta (FR β) as well as other macrophage marker expressions were measured using FACS.

Intra-articular injections with triamcinolone strongly enhanced FR β + macrophage activation and fully prevented osteophyte formation. There were no beneficial effects of the corticoid steroid against cartilage degradation or subchondral bone sclerosis. In *in-vitro* cultures triamcinolone strongly induced the monocyte-macrophages differentiation towards CD163+ and FR β + cells, specifically in GM-CSF stimulated (M1) cultures. Addition of triamcinolone to M-CSF stimulated (M2) monocytes showed enhanced IL10 expression on mRNA level.

In conclusion triamcinolone enhanced FR β expression in monocytes that were induced to macrophage differentiation. The triamcinolone injections stimulate synovial macrophage activation and triggers the macrophages towards a more anti-inflammatory subtype.

S11

Canine chondrodystrophic intervertebral disc disease (Hansen type I disc disease)

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Intervertebral disc disease (IVDD) is the most common spinal disease in dogs. Chondrodystrophic dogs, which have disproportionably short and curved limbs, are predisposed to Hansen type I IVDD and of these the miniature Dachshund is over represented [1,2], is more likely to be presented at an earlier age [3] and is at greater risk of a severe spinal cord injury [4]. The tendency for IVDD in Dachshunds is inherited [5,6] and a major locus on chromosome 12 harbours genetic variations affecting the development of intervertebral disc calcification [7]. Hansen type I disc degeneration is thought to occur because of loss of notochordal cells which produce proteoglycans which "hold water" in the disc. Chondrodystrophic dogs have a primary deficiency of notochordal cells, a study found that large notochordal cells in the nucleus pulposus of chondrodystrophic dogs formed 13% of the cell population in young dogs and fell to 0.4% in adults, whereas they were the predominant cell type in the nonchondrodystrophic dogs at all ages [8]. Thus chondrodystrophic dogs suffer early degenerative changes in the disc and a concomitant reduction in proteoglycan content, increased collagen, and loss of water content making the discs likely to herniate [8]. Certain lifestyle factors may increase or decrease risk of IVDD and this is currently under investigation. There is a suggestion that exercise (including stair climbing) reduces the incidence of disc calcification [9]. By contrast it has been hypothesized that obesity/lack of postural muscle strength may increase risk. Dachshunds with intervertebral disc extrusion had significantly smaller cross sectional area and greater fat infiltration in the epaxial muscles (muscles which lie dorsal to the horizontal septum of the vertebrae which mobilize and globally stabilize the trunk [10]) compared to dogs presenting with fibrocartilagenous embolism (another acute onset intervertebral disc related spinal disease) [11]. In addition chondrodystrophic dogs may have increased risk of IVDD if they have a more extreme conformation e.g. Dachshunds that have a longer back and shorter limbs are more at risk [12] and breeds with a comparatively

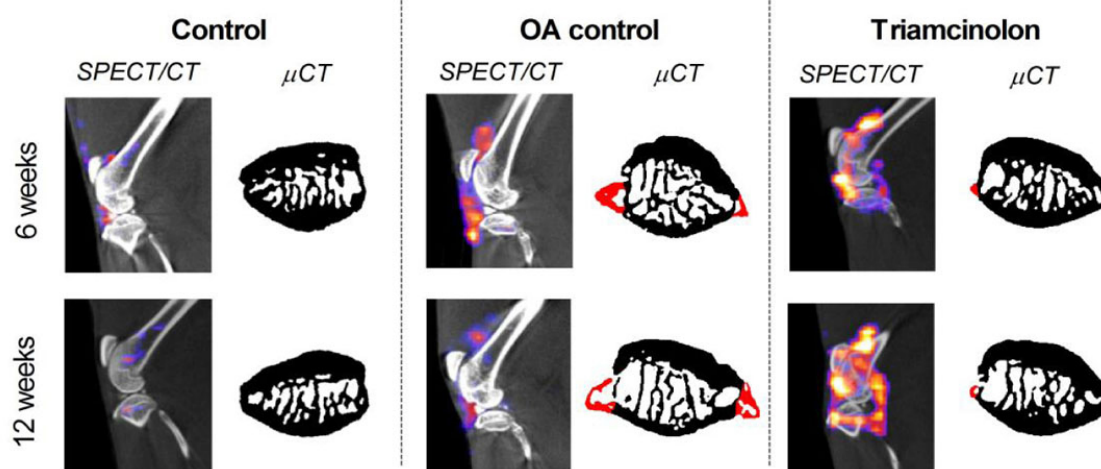


Figure 1(abstract S10) Macrophage activation determined after injection of ¹¹¹In-DTPA-folate using SPECT/CT in Papain induced osteoarthritis (OA) combined with moderate exercise. Representative sagittal SPECT/CT images of knee joints from representative animals per experimental group. CT images shown in black and white were used for anatomical reference, the SPECT images are shown in colour. Patellar bone is shown with osteophyte formation highlighted in red

heavy head such as the Bassett Hound may be more at risk of cervical disc disease. Breeds with a tendency for kyphoscoliosis such as the French Bulldog may be more at risk of IVDD in the IVDs adjacent to a vertebral malformation [13,14]. This presentation details the pathogenesis, clinical presentation, diagnosis and treatment of IVDD in chondrodystrophic dogs.

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S12

Collaboration and partnership in orthopaedics and musculoskeletal research: academia, industry, health services, and patients

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The main activity of Orthopaedic Research UK (ORUK) is to provide funding to centres of excellence to conduct research in the field of orthopaedics, in order to benefit patients suffering from bone and joint disorders. However, the majority of the grants awarded will not make it to the market as products, surgical techniques or novel rehabilitation approaches. Therefore, in general, grants are made with no expectation of a financial return and very often with no measurable patient benefit. But in the event when the researchers manage to generate intellectual property (IP)

and a commercial opportunity, it is expected that the funder should also share the financial benefits in order to reinvest the money back into its pursuit of its mission.

Since 2004, ORUK has invested over £8.2m on 120 projects in 37 institutions, which has thus far generated nil return on investment. Even though so far ORUK has managed to file three patents – in 2009, 2013 and 2014 – the organisation has yet to see the long-term benefits for the stakeholders. ORUK is addressing a perceived lack of efficiency to show impact on patients by implementing a new approach through a specific translation research funding (TRF) programme within its strategy. ORUK is aiming to promote the innovation process to ensure that the money invested in research is given the best opportunity to translate into meaningful outcomes.

S13

Musculoskeletal health and osteoarthritis in the UK army – the ADVANCE study (Armed Services Trauma Rehabilitation Outcome Study)

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Trauma is a well recognised risk factor for the future development of osteoarthritis (OA). The Armed Services Trauma and Rehabilitation outcome study (The ADVANCE study) is a 20 year cohort study comparing medical and psychosocial outcomes of military personnel both exposed and not exposed, to significant trauma.

The Bio-Mil-OA study, a sub-study of the ADVANCE study, is an ideal opportunity to investigate the predictive value of biomarkers in joint pain and osteoarthritis.

The ADVANCE study is a 20 year cohort study of 600 combat casualties and 600 matched non exposed participants investigating the predictive value of biomarkers and trauma on the long term development of pain and OA in the hip and knee. Validated serum biomarkers for OA, knee and hip radiographs and patient reported outcomes for pain and function will be taken at baseline and at 5 years.

The predictive value of the biomarkers in predicting OA development and progression and joint pain in those exposed to different levels of trauma will be investigated using quantitative immunoassays for catabolic markers of cartilage matrix degradation.

S14

Physical therapy and exercise in osteoarthritis prevention

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Exercise encompasses physical activity (habitual, sporting), and exercise programmes to improve and maintain joint health. Clinical guidelines recommend exercise for osteoarthritis (OA) e.g. NICE, EULAR, OARSI. Benefits of moderate exercise include weight control (obesity is a known risk factor for OA) and joint health (beneficial for cartilage). Specific exercises aim to achieve optimal biomechanics to protect joints (joint alignment, load reducing strategies) and improve muscle strength, endurance, power, flexibility and co-ordination. Other physiotherapy principles include sport/task specific exercises, personalised medicine (exercises tailored for the individual) and neuromuscular control of movement (screening and retraining using specific exercises). Manual therapy techniques (pain management, mobilisations, muscle stretching) can improve exercise outcomes. Effects of exercise on pain and function are comparable with those for non-steroidal anti-inflammatory drugs. Exercise forms part of biopsychosocial management, using tailored, patient centred interventions based on assessment, with shared decision making. Three levels of prevention include: primary (preventing injury and onset of OA), secondary (preventing progression of OA) and tertiary (managing

complicated, long-term health problems). The Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis is focussing on secondary prevention of progression of injury and/or overuse to OA. Biomechanical and neurophysiological mechanisms of abnormal movement and joint loading are investigated using 3D motion analysis and electromyographic techniques, and evidence is emerging that mechanistic-based exercises can correct abnormal movement.

Movement screening tools in clinical/field environments are used increasingly to assess movement control and functional performance, primarily in sport, to predict injury and/or inform intervention. Robustness of screening tools is variable, in terms of reliability, validity and prediction of injury risk. Consensus is needed for terminology and establishing which screening tests are appropriate for specific cohorts and movement problems.

High quality longitudinal trials are needed to ensure effective use of exercise for OA prevention. Activity needs to be maintained for long-lasting effects but adherence to changing lifestyle remains a major challenge. For exercises targeting movement problems, studies need to elucidate which elements, modes, doses, and frequency and duration of exercise are optimal for specific joints and body regions.

It remains unknown whether exercise can influence disease pathogenesis and progression. Evidence of cost-effectiveness of exercise as a clinical intervention for OA is also needed. Understanding and overcoming barriers to exercise and enabling access will be crucial for widespread uptake of exercise. Translation research is needed to determine how to change practice and influence GP referral to exercise programmes.

S15

Surgeon General's bone health project: translation of research to mitigate injury risk in Royal Marines recruits

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Overuse injury, including stress fracture (SF), in military training results in significant economic losses and individual discomfort. The 32-week Royal Marine (RM) training programme is recognised worldwide as the most arduous initial training programme. Research has failed to fully identify bone density and structural differences between SF personnel and controls due to inadequate adjustment for confounding factors and poor sample size. Moreover, whilst associations have been reported between serum 25-hydroxyvitamin-D (25(OH)D) and SF risk, the threshold for this effect remains unclear. This programme determined if 25(OH)D concentrations were associated with SF risk during military training, and investigated physical and bone differences between matched (age, body size and aerobic fitness) injured and uninjured recruits, to inform future policy and practice.

RM recruits (n=1090; males aged 16-32 y) were followed through training, where 78 recruits (7.2%) suffered 92 SF in total. Anthropometric measures and aerobic fitness were assessed at week-1. Lumbar spine (LS), femoral neck (FN) and whole body (WB) Bone mineral density (BMD) (Dual X-ray Absorptiometry), and tibial bone parameters (peripheral Quantitative Computer Tomography), were measured in matched (injured vs. uninjured) pairs. Venous blood samples drawn at weeks 1, 15 and 32, were analysed for serum C-terminal peptide concentration (as a marker of bone resorption), 25(OH)D and PTH.

Age (<18 y; >27 y), body mass (<65 kg) and fitness were associated with injury risk (P<0.05). Recruits with a baseline 25(OH)D concentration <50 nmol.L⁻¹ had a higher SF incidence than recruits with 25(OH)D concentration >50 nmol.L⁻¹ ($\chi^2_{(1)}=3.564$, $p=0.042$; odds ratio 1.6 (95% CI 1.0-2.6)). There were weak inverse correlations between week-15 25(OH)D and PTH concentrations ($r=-0.209$, $p<0.001$) and week-32 ($r=-0.214$, $p<0.001$), but not at baseline. BMD at the LS, WB and FN were lower in SF compared with uninjured recruits (ANCOVA, $P<0.001$). Structural differences between SF and uninjured recruits were evident in all slices of the tibia, but most prominently at the 38% slice. There was a negative correlation between bone cross-sectional area and BMD at the 38% tibial slice. There was no difference in CTx concentration between SF and uninjured recruits at any stage of training.

Thus, differences in anthropometric, aerobic fitness, baseline serum 25 (OH)D concentration, bone mass and bone structure, between SF and uninjured recruits, provided evidence to inform changes in RM physical selection standards to reduce injury. Further work examining the effects of vitamin D supplementation on SF risk has been initiated to support recruit health and wellbeing.

S16

Vitamin D and bone health

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Throughout the life-cycle, the skeleton requires optimum development and maintenance of its integrity to prevent fracture. Bones break because the loads placed upon them exceed the ability of the bone to absorb the energy involved. It is now estimated that 1:3 women and 1:12 men over the age of 55 years will suffer from osteoporosis in their lifetime and in the UK, at a cost in excess of £1.7 billion per annum to the exchequer. The pathogenesis of osteoporosis is multi-factorial. Both the development of peak bone mass and the rate of bone loss are determined by key endogenous and exogenous factors. Calcium supplements appear to be effective in reducing bone loss in late menopausal women (>5 years post-menopause), particularly in those with low habitual calcium intake (< 400mg/d). In younger postmenopausal women, who are not vitamin D deficient, vitamin D supplementation has little effect on BMD. However, vitamin D and calcium supplementation studies have been shown to reduce fracture rates in the institutionalized elderly but there remains controversy as to whether supplementation is effective in reducing fracture in free-living populations. Re-defining vitamin D requirements in the UK is urgently needed since there is evidence of extensive hypovitaminosis D in the UK. Low vitamin D status is associated with an increased risk of falling and a variety of other health outcomes and is an area that requires urgent attention. The role of other micronutrients on bone remains to be fully defined, although there are promising data in the literature for a clear link between vitamin K nutrition, dietary protein and dietary alkali on skeletal integrity including fracture reduction.

S17

What can we learn about joint degeneration from rare and orphan diseases?

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William Harvey, the great English physician of the 17th century, observed *"Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows tracings of her workings apart from the beaten paths; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature, by careful investigation of cases of rarer forms of disease"* [1]. The history of medical science has proven Harvey correct; studying severe phenotypes of rare diseases has helped elucidate pathophysiological mechanisms of more common disorders and led to the identification of new biomarkers and therapeutic targets [2]. For example the development of bisphosphonates, the most successful class of bone active agent, owes a debt to research on hypophosphatasia. More recent research on rare bone syndromes has helped identify new targets to inhibit bone resorption and stimulate bone formation including cathepsin K and sclerostin. Drugs against both these targets are now in clinical trials. Osteoarthritis (OA) is a major cause of morbidity and disability. It is also the only major musculoskeletal disorder for which there are no effective therapies, other than pain relief and eventual joint replacement. Recent studies on rare cartilage syndromes have identified some potential therapeutic target including GDF5 and lubricin. Research from our laboratory has focussed on the early onset, aggressive joint destruction which occurs in the osteoarthropathy of the rare disease alkaptonuria (AKU). AKU is a single gene defect in tyrosine metabolism, which is characterised by ochronosis, the deposition of pigmented polymers in

connective tissues particularly cartilage. Studying tissue samples from AKU patients and from AKU mouse models has revealed significant parallels with the pathophysiology of OA. We have discovered several previously unidentified microanatomical changes in AKU joints which were subsequently recognised in joint degeneration associated with OA and ageing. Of these the most significant are high density mineralised protrusions (HDMs). These novel microanatomical structures arise via the extrusion of a mineralisable matrix through cracks in the subchondral plate. Formation of HDMs constitutes a previously unrecognised mechanism of joint destruction [3].

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S18

Animal models and systems biology approaches for the functional validation of genetic determinants of skeletal diseases

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Rare skeletal diseases are a diverse group of diseases that primarily affect development of the skeleton. There are more than 450 unique phenotypes that, although individually rare, have an overall prevalence of at least 1 per 4,000 children. Pseudoachondroplasia (PSACH) and multiple epiphyseal dysplasia (MED) are skeletal diseases caused by missense mutations/deletions in the genes encoding important cartilage extracellular matrix proteins (ECM), and are characterized by disproportionate short stature, joint pain and early-onset osteoarthritis.

In-depth characterization of MED and PSACH mouse models has revealed that endoplasmic reticulum (ER) stress, reduced cell proliferation and abnormal ECM assembly are important pathological consequences of mutant protein expression. Ongoing work aims to consolidate data from other models of skeletal disorders using a systems biology approach as part of the EU FP7 SYBIL (Systems biology for the functional validation of genetic determinants of skeletal diseases) project, in order to gain a mechanistic understanding of disease processes and to deliver new and validated therapeutic targets.

Key to delivery of new targets and therapies is the identification of relevant disease biomarkers, which will allow the monitoring of responses to therapeutic interventions. This is particularly critical for skeletal diseases, for which biopsy material is not readily accessible. We have identified differences in the extractability of a number of ECM components from the cartilage of MED and PSACH mouse models, relative to controls. The differences in extractability of these proteins (which include FACIT collagens (types XII and XIV), tenascins (C and X), and fetuin A) may represent differences in the stability of these proteins within the cartilage ECM, which might potentially be exploited for use as biomarkers of disease progression. We are currently using biochemical and mass spectrometry analysis of easily obtained biological samples such as blood, urine and cell culture medium in order to identify and validate novel biomarkers for skeletal diseases.

S19

Intervertebral disc degeneration therapies in human

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Low back pain (LBP) is one of the most common musculoskeletal disorders, with an estimated 84% of the population experiencing LBP at some point in

their lifetime. As with most musculoskeletal disorders, the prevalence of LBP increases with age, suggesting incidences of LBP are likely to increase in the future due to a global aging population, changes in lifestyle and occupational stresses. Although the causes of LBP are multifactorial, increasing evidence implicates intervertebral disc (IVD) degeneration as a major contributor, with loss of IVD integrity leading to the destabilization of the spinal motion segment, resulting in pain and disability.

The IVD is a complex structure that allows movement between adjacent vertebrae and sustains the load applied through the spine. It consists of the peripheral annulus fibrosus (AF), a ligamentous lamellar structure composed predominantly of type I collagen fibres, and the central nucleus pulposus (NP), a highly hydrated structure, composed of the proteoglycan aggrecan, interspersed with type II collagen fibres. Only 1% of the IVD volume is occupied by its constituent cells, but they assume a key role, as they maintain IVD homeostasis. In degeneration there is an alteration in NP cell biology leading to diminished cell numbers and altered cell function resulting in an imbalance between matrix synthesis and degradation, particularly within the NP.

Current medical treatments for IVD degeneration rely on conservative therapies (e.g. pain relief, exercise therapy) and, when these fail, surgery. Surgical treatments such as spinal fusion and disc replacement have shown satisfactory results in alleviating pain, but are not devoid of complications and long-term clinical outcomes still remain poor. Thus, there is an urgent need for alternative therapies focussed on correcting the underlying pathogenesis and aberrant cell biology of IVD degeneration. As such many researchers, including ourselves, are focussing on the development of novel cell-based therapies. However, in order for these to be successful an appropriate cell source for implantation and tissue regeneration must be identified.

In this presentation we discussed the pathophysiology of IVD degeneration, efforts to elucidate the phenotype of human IVD cells and how this has allowed development of mesenchymal stem cell (MSC)-based therapies for IVD regeneration. In particular it focused on our efforts to identify the optimal MSC source and growth factor to direct differentiation and enhance tissue formation, as well as the influence microenvironment has on regeneration strategies.

S20

Carbon nanotubes: a promising tissue engineering approach for *in vitro* cultivation & differentiation of primary canine articular chondrocytes

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Development of biocompatible materials has great potential in biomedical engineering both for *in vitro* studies as well as for *in vivo* applications. Two- and three-dimensional carbon nanotube (CNT) substrates imitating and providing an extracellular matrix-like structure are promising constructs as cell-supporting scaffolds. Lately, they have received considerable interest in tissue engineering; however, cellular responses to nanoscale stimuli need to be better understood.

Here, we present the preliminary results on the effect of CNT-based scaffolds on the proliferation and arrangement of primary canine chondrocytes (PCCs). We aim to develop scaffolding materials for the *in vitro* cultivation of normal and neoplastic cells with the ultimate objective of using them for applications such as tissue implants in cartilage repair and tissue regeneration after surgical intervention.

In the proposed studies we aim to use an aerogel network of CNTs that has been drawn from a vertically aligned array as a synthetic substrate

for the growth and alignment of primary canine chondrocytes. This aerogel consists of CNTs that are aligned parallel to the major axis of the CNTs; they have exceptionally low densities, are electrically and thermally conductive whilst maintaining very high tensile strength and elasticity. We are studying the cell growth, adhesion, morphology, viability and metabolism of cells seeded onto CNT substrates.

Preliminary results to date have revealed that PCCs are capable of proliferating on CNT-based scaffolds, although the cell viability seems to be slightly decreased in comparison to the conventional 2D cell culture. Moreover, our nanosubstrates are able to induce directional cell growth

of PCCs via aligning cells along CNTs. The latter is essential for *in vivo* application of nanosubstrates in tissue regeneration.

Cite abstracts in this supplement using the relevant abstract number, e.g.: Matta-Domjan *et al.*: Carbon nanotubes: a promising tissue engineering approach for *in vitro* cultivation & differentiation of primary canine articular chondrocytes. *BMC Musculoskeletal Disorders* 2015, 16 (Suppl 1):S20